REMARKS

I. Status of Claims.

This application has been reviewed in light of the Office Action dated July 3, 2002. Claims 1-6 are presently pending. Claims 1, 3, 4 and 5 are amended in a manner that is believed to overcome rejections contained in the pending Office Action. No new matter or issues are believed to be introduced by these amendments. Support for the amendments is found throughout the specification and drawings.

II. Claims 1-6 rejected under 35 USC 112, first paragraph.

The Examiner in the official office action date July 3, 2002 rejected claims 1-6 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claim invention. The Examiner states that the specification while being enabling for a method of administering to a mammal a therapeutically effective amount of an inhibitor of dipeptdyl peptidase (DPIV) and physiologically acceptable adjuvant and or excipients for reducing in said mammal activity of endogenous DPIV Applicants have considered the Examiners rejection but must respectfully traverse this rejection.

The claimed subject matter of the instant invention is directed to a method of raising the blood sugar level in a mammal having hypoglycemia by reducing degradation of glucagon. The instant specification identifies several compounds that have been found to be effective in this therapeutic method. The Examiner states that "[w]ith only knowing these few inhibitors of DPIV, it is clear that such broad claims are not enabled by the instant specification when one of ordinary skill in the art is only given these limited amount of inhibitors." The instant claims are

directed to a method of using compounds that inhibit DPIV to raise glucose blood levels. The method, not the formula or name, is the invention and this have been more than fully enabled, see Petisi v. Rennhard, 363 F. 2d 90, 150 USPQ 669 (C.C.P.A. 1966). Further, Applicants would drawn the Examiner's attention to numerous references related to various compounds and their mechanism of action in the inhibition of DPIV contained within the specification. These references that have been incorporated by reference more than sufficiently enable the Applicants' invention, *In re* Howarth, 654 F.2d 103, 210 USPQ 689, 692 (C.C.P.A. 1981). Applicants would respectfully request withdrawal of this rejection.

III. Rejection of claims 1-5 under 35 USC 112, second paragraph.

Claims 1-5 under 35 U.S.C. 112, second paragraph, were rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, it was stated that the phrase " an effector for reducing enzymatic activity of DPIV and DPIV analogous enzymes" in claim 1 was confusing and therefore the rejected claims failed to clearly point out Applicants' invention. As the Examiner as suggested, Applicants have amended the claims to clearly specify that the effectors are inhibitors that act to reduce enzymatic activity in accordance with the description in the specification beginning with the first paragraph on Page 1.

With regard to claim 1," hypolycameia" and " effector" are amended in a manner that is believed to overcome the rejection. Reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

With regard to claim 2, claim 1 from which it depends has been amended in a manner that is believed to overcome the rejection. Reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

With regard to claim 3 "effector" is amended in a manner that is believed to overcome the rejection. Reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

With regard to claim 4, " effector" is amended in a manner that is believed to overcome the rejection. Reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

With regard to claim 5, " effector" is amended in a manner that is believed to overcome the rejection. Reconsideration and withdrawal of this rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

With regard to claim 6, Applicants would respectfully urge that claim 6 as presently set forth complies with the requirements of 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Accordingly, Applicants respectfully submit that the claims as amended fully satisfy the requirements set forth under 35 USC Section 112, second paragraph. Applicants have amended the above claims merely to meet the requirements of 35 U.S.C. §112, second paragraph and to make explicit what was implicit within the pending claims. Reconsideration in light of the change and withdrawal of this rejection is respectfully requested.

IV. Claims 1-6 rejected under 35 USC 102 (b).

Claims 1-6 were rejected under 35 USC 102 (b) as being anticipated by WO 97/40832 to Demuth et al (Demuth). The Examiner states that the abstract of Demuth teaches the use of DPIV inhibitors for lowering the blood glucose level in mammals. The Applicants have considered this rejection but must respectfully traverse. Demuth discloses the use of DPIV inhibitors for lowering the blood glucose level in mammals. The Applicants' claimed invention is directed to a method of using DPIV inhibitors to raise the blood glucose level in a mammal having hypoglycemia. The use of DPIV inhibitors to raise blood glucose in mammals is not disclosed. It is therefore respectfully requested that this rejection be withdrawn.

V. Claims 1-6 were rejected under 35 USC 103(a)

The Examiner rejected claims 1-6 under 35 USC 103(a) as being obvious over Chen et al. in view of Efendic and Bachovchin et al. The Applicants respectfully traverse this rejection.

Chen (U.S. patent 5,512,549) concerns glucagon-like insulinotropic peptide, GLP-1(7-37), and its analogs and derivatives. It should be clearly noted that GLP-1 is not glucagon. The compounds of Chen are claimed to stimulate the secretion or biosynthesis of insulin in poorly functioning beta cells and to therefore be useful in treating Type II diabetic patients. While Chen sets forth the proposition that GLP-1 (7-37) is readily inactivated by DP IV, it does not suggest the claimed invention of the present application. Specifically, it makes no statement concerning whether glucagon can serve as a DP-IV substitute. Chen's compounds stimulate peripheral glucose disposal thereby lowering blood glucose. However, the presence of glucagon has the opposite effect since it raises hepatic glucose output. GLP-1 has been known as a DP IV substrate since 1993 (Mentlein, R., Gallwitz, B., and Schmidt, W.E. (1993)). It is also known that Dipeptidyl Peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1

(7-36) amide, peptide histidine methionine and is responsible for their degradation in human serum (Eur. J. Biochem. 214, 829-835.).

However, glucagon has not been known to be a DP IV substrate and this discovery is a central feature to the instant invention. Chen neither discloses nor teaches that glucagon is a DP IV substrate. It is the present invention which provides the first teaching regarding the enzymatic actions of DP IV on glucagon. And, it also the first to teach that a DP IV enzymatic inhibitor can be used to stimulate endogenous glucose production via glucagon stabilization. It is alleged in the Office Action that Chen makes it clear that glucagon increases blood glucose, however, Applicants respectfully but strongly disagree. The metabolic pathway of glucagon to glucose is a well established understanding that is routinely known by those skilled in the art. While Chen may be restating this well known medical principle, Chen falls far short of stating that a DP IV enzymatic inhibitor can be used to stabilize glucagon resulting in an increase in glucagon levels and that this increase will lead to elevated glucose levels. It is Applicants disclosure that makes this leap, not Chen. Finally, it is imperative to recognize that Chen's glucagon-like peptides, that are inactivated by DP IV, are compounds that have the opposite effect of glucagon in that they reduce glucose by stimulating insulin secretion (See Chen Col 3, Lines 22-25). If anything, Chen teaches away from the principles of Applicants' invention.

While Bachovchin (U.S. Patent 4,935,493) lists compounds that are dipeptidyl-peptidase IV inhibitors, Bachovchin is directed to modulating immune responses and does not teach their use in affecting glucose levels in an organism. Thus, the teaching of Bachovchin does nothing to relieve the teaching deficiencies of Chen and therefore their combination fails to teach or make obvious the principles of the present application.

While Efendic (U.S. Patent 6,006,753) teaches that hypoglycemia is a dangerous disease, that in itself is routinely known by those skilled in the art. Efendic's administration of GLP-1 or related substances is far removed from the present invention. Efendic thus lends nothing to relieve the deficiencies of either Bachovchin or Chen taken individually or combination. Accordingly, the combination of the teachings of Chen, Bachovchin and Efendic do not and can not lead to, or suggest the principles presented in the present application. With careful consideration, it will be appreciated that the rejection of claims 1-6 as being obvious in light of the teachings of the above cited patents is unsustainable. Applicants respectfully request that this rejection be withdrawn.

VI. Claims 1-6 rejected under 35 USC 103(a)

Claims 1-6 were rejected under 35 USC 103(a) as being unpatentable over WO 97/40832 (Demuth) taken with Galloway et al., US Patent 5,705,493 (Galloway). The Examiner states that it is not clear if glucagon is administered with the DPIV inhibitor in Demuth.

The Applicants would respectfully urge that the abstract of this reference teaches the use of DPIV inhibitors for lowering the blood glucose level in mammals and therefore the administration of glucagon would be contrary to the teachings of Demuth. The teachings of Demuth do not support an obviousness rejection of Applicants' claimed invention.

The Examiner, in the alternative, states that the secondary reference of Galloway teaches that GLP-1 is well known in the art to be used to treat hypoglycemia. The Applicants would respectfully disagree. A complete reading of Galloway discloses that GLP-1 can be used within a method of treatment for maturity onset diabetes mellitus in mammals. Unlike the instant invention, Galloway is concerned with the treatment of hyperglycemia. Neither Demuth nor

Galloway are instructive as to the Applicants' claimed invention. Applicants would therefore respectfully requested that this rejection be withdrawn.

CONCLUSION

In accordance with 37 CFR 1.21 (c)(1)(ii) a marked up version of the amendment claims is attached as Appendix A to this response. For the foregoing reasons and amendments, Applicants believe this application is in condition for allowance which is respectfully requested.

Respectfully submitted,

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Appendix A

1. (AMENDED) A method of raising the blood sugar level in a mammal having hypoglyc[a]emia by reducing degradation of glucagon, said method comprising administering to-said mammal a therapeutically effective amount of an [effector] inhibitor for reducing enzymatic activity of dipeptidyl peptidase (DP IV) and DP IV-analogous enzymes.

3. (AMENDED) The method of claim 1, wherein the [effector] inhibitor is selected from the group consisting of DP IV enzyme inhibitors, substrates of DP IV, pseudo-substrates of DP IV, inhibitors of DP IV expression, proteins that bind DP IV or antibodies to DP IV and combinations thereof.

4. (AMENDED) The method of claim 1, wherein the [effector] inhibitor for reducing enzymatic activity is employed together with glucagon or analogues thereof.

5. (AMENDED) The method of claim 1, wherein the [effector] inhibitor for reducing enzymatic activity is employed in combination with physiologically acceptable adjuvants and/or excipients.